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The absolute configuration of sertraline (Zoloft) hydrochloride

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Abstract

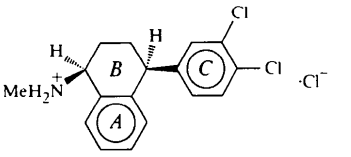
We report the results of a crystal structure determination of the *S,S* stereoisomer of sertraline (Zoloft) hydrochloride {[(1*S-cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl]methylammonium chloride, $C_{17}H_{18}Cl_2N^+\cdot Cl^-$}, which is the active form used as an antidepressant in humans. The conformation of sertraline has two planar phenyl rings that are approximately perpendicular to each other, and an unsaturated ring in a half-chair conformation.

Comment

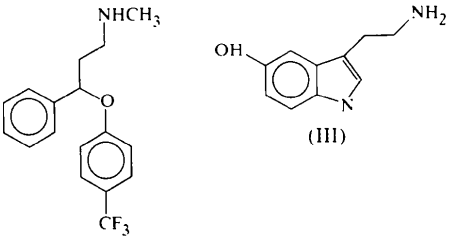
Many cases of depression can be related to changes in the neurochemistry of three monoamine neurotransmitters that are derivatives of amino acids, *i.e.* serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (noradrenaline, NA) and dopamine. Evidence points to the role of two of these neurotransmitters, serotonin and norepinephrine, in depression (Nemeroff, 1998). Serotonin released at synapses is usually promptly removed by a transport protein for use in neurotransmitter processes. Serotonin specific (or selective serotonin) reuptake inhibitors (SSRIs) are a highly effective class of antidepressant drugs, due to their having milder side effects than their predecessors, *i.e.* monoamine oxidase inhibitors (MAOs) and tricyclic antidepressants (TCAs). SSRIs preferentially inhibit serotonin reuptake in the brain, compared with NA or dopamine, by binding to the serotonin uptake carrier protein; this increases serotonin transmission and its concentration in nerve synapses. It is not yet clear whether the substrate (serotonin) binding site in the transport protein is the same as the SSRI inhibitor binding site. The first SSRI to be marketed was fluoxetine (Prozac) and although sertraline's mechanism appears similar to that of fluoxetine, sertraline is more selective and more potent in inhibiting serotonin uptake.

In sertraline hydrochloride, (I), all bond distances and angles fall within expected ranges and show no unusual features. The packing of the molecules in the unit cell shows the chloride anion, Cl3, situated along the *b* axis and near $z = \frac{1}{4}$ and $\frac{3}{4}$; it lies between the amino-N atom of two symmetry-related sertraline molecules [Cl3···N1 = 3.103 (5) Å and Cl3···N1($-x$, $y-\frac{1}{2}$, $\frac{3}{2}-z$) = 3.083 (5) Å]. The dichlorophenyl rings are arranged in planes along the [100] direction at approximately $z = 0$ and $\frac{1}{2}$. The rings in different planes are shifted in the [010] direction. They are related such that the Cl atoms of two symmetry-related molecules in the different planes face each other. The interaction between a reference (x, y, z) molecule and a symmetry mate at ($\frac{1}{2}+x$, $-y-\frac{1}{2}$, $-z+2$) results in the Cl···Cl distances Cl1···Cl2 = 4.172 (4) Å and Cl2···Cl1 = 4.017 (4) Å.

Since the effectiveness of SSRIs stems from their ability to replace 5-HT in the serotonin transporter protein, a comparison of the structures of sertraline and fluoxetine (Prozac), (II), with 5-HT, (III), provides useful structural information regarding the activity of these compounds. Analysis of common features of all serotonin-receptor ligands has been described already (Dalpiaz *et al.*, 1996) and an attempt to define the structure of the pharmacophore for SSRIs has been made using calculated minimum-energy conformations among the inhibitors (Chang *et al.*, 1993). Both studies concluded that a key factor for the activity is the distance between the center of the aromatic ring and the basic N atom.



(I)



(II) (III)

The crystal structure of fluoxetine (Prozac) has been described (Robertson *et al.*, 1988). A crystallographic study of sertraline was performed earlier (Welch *et al.*, 1984), but not published. Therefore, comparing our structural results on sertraline with those on fluoxetine, we note the following features:

(i) the molecules have three domains consisting of (*a*) a quaternary nitrogen moiety, (*b*) a hydrophobic phenyl ring and (*c*) an aromatic ring with electronegative halogen atoms.

(ii) They both have chiral carbon centers; fluoxetine is sold as a racemic mixture with both enantiomers present, while the active form of sertraline is the *S,S* stereoisomer.

(iii) Fluoxetine has a dipole moment of 1.30×10^{-31} C m, while the sertraline dipole moment is 4.37×10^{-31} C m (Pople & Beveridge, 1970).

(iv) The amino-group side chain in both fluoxetine and sertraline provide for a positively charged group to interact with negatively charged amino acid residues in the transporter protein. This positive charge on the amino group is enhanced by the electron-withdrawing effect of the halogen atoms in fluoxetine and sertraline.

(v) The hydrophobic phenyl group and the halogen-substituted phenyl ring on fluoxetine are perpendicular to each other, as are the analogous rings *A* and *C* in sertraline. As determined by X-ray diffraction studies, the conformation of serotonin, (III), itself shows the amino-containing side chain of serotonin to be perpendicular to the indole ring (Thewalt & Bugg, 1972).

(vi) The distance from the 'center-of-mass' of each molecule to an extreme halogen is about the same, approximately 6 Å. In fluoxetine, about 4 Å separates the center-of-mass (the chiral carbon) and the N atom; in sertraline, the distance is about 3 Å.

(vii) Both molecules have a separation of approximately 6.5 Å between the center of the halogen-substituted phenyl ring and the amino N atom.

The results of this crystal structure determination help in defining the structural similarities and differences between fluoxetine and sertraline. SSRIs have revolutionized the treatment of depression and an understanding of the structure–function relationship of these compounds is important for the broader goal of understanding the neurobiology of depression.

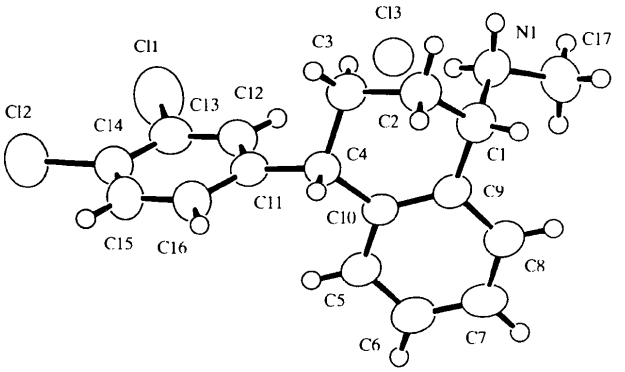


Fig. 1. The molecular structure of (I) shown with ellipsoids at the 50% probability level.

Experimental

The *S,S* stereoisomer of sertraline was recrystallized from an ethanol–petroleum ether solvent system. Using NMR methods, the solution structure was confirmed to be the same as that in the solid state.

Crystal data

$C_{17}H_{18}Cl_2N^+ \cdot Cl^-$
$M_r = 342.70$
Orthorhombic
$P2_12_12_1$
$a = 7.994\ (6)$ Å
$b = 8.371\ (7)$ Å
$c = 25.142\ (20)$ Å
$V = 1682.4\ (4)$ Å^3
$Z = 4$
$D_x = 1.353$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 21 reflections
$\theta = 6$–$20°$
$\mu = 0.537$ mm^{-1}
$T = 293$ K
Prism
$0.30 \times 0.20 \times 0.10$ mm
Colorless
Crystal source: a gift from Pfizer Inc. (New York)

Data collection

Crystal Logic-modified Syntex *P*21 diffractometer
θ–2θ scan
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.852$, $T_{max} = 0.946$
4787 measured reflections
4643 independent reflections
2230 reflections with $F > 3\sigma(F)$
R_{int}: see below
$\theta_{max} = 28°$
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 11$
$l = -33 \rightarrow 33$
3 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on *F*
$R = 0.058$
$wR = 0.049$
$S = 1.391$
2230 reflections
192 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o)]$
$(\Delta/\sigma)_{max} = 0.010$
$\Delta\rho_{max} = 0.255$ e Å^{-3}
$\Delta\rho_{min} = -0.410$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: refinement of the other polarity gave the same *R* factors ($R = 0.058$, $R_w = 0.049$)

The equivalent reflections were not merged. The absolute configuration was determined following a procedure described previously (Byrn & Strouse, 1991). The refinement program models the sample as an inversion twin, where the 'twinning parameter', *p*, represents the fraction of the sample that is inverted with respect to the atomic model chosen, *i.e.* $(F_{calc})^2 = (1-p)(A^2 + B^2) + p(A_{inv}^2 + B_{inv}^2)$, where *A* and *B* are the real and imaginary parts of the structure factor calculated on the basis of the atomic model, and A_{inv} and B_{inv} are the real and imaginary parts of the structure factor based on the inverted model. Flack has used the same parameter for enantiomer–polarity estimation (Flack, 1983). In the current structure determination, *p* refined to a value of 0.00 (15), providing a substantial indication that the model refined corresponds to the correct enantiomer. As a test of the validity of this refinement procedure, the coordinates were inverted and in this case, *p* refined to a value of 1.00 (15), indicating that the alternative model was the incorrect enantiomer.

Data collection: Crystal Logic software (Byrn & Strouse, 1991). Cell refinement: Crystal Logic software. Data reduction: Crystal Logic software. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: Crystal Logic software. Molecular graphics: *CAOS*

(Camalli & Spagna, 1994). Software used to prepare material for publication: *CAOS*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1083). Services for accessing these data are described at the back of the journal.

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1:2 Complexes of chloranilic acid with pyrimidine and pyrazine

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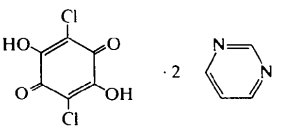
Abstract

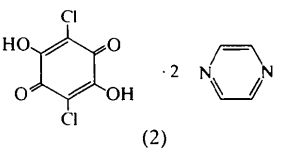
The hydrogen-bonded 1:2 complexes of chloranilic acid (2,5-dichloro-3,6-dihydroxy-*p*-benzoquinone) with pyrimidine [(1), $C_6H_2Cl_2O_4\cdot 2C_4H_4N_2$] and pyrazine [(2), $C_6H_2Cl_2O_4\cdot 2C_4H_4N_2$] were prepared and their crystal structures determined at room temperature. In both complexes, the chloranilic acid molecules lie on inversion centres and in each complex, the two components are held together by O—H···N hydrogen bonds with short O···N distances of 2.615 (2) Å for (1) and 2.590 (4) Å for (2).

Comment

Several hydrogen-bonded complexes in chloranilic acid–amine 1:1 systems were studied by IR, NMR and UV (Issa *et al.*, 1991; Habeeb *et al.*, 1995). Habeeb *et al.* (1995) reported that the hydrogen bonds formed between chloranilic acid and amines vary from an N—H···O to an N···H—O type with decreasing pK_a values of the amines. Recently, we reported the crystal structure of the 1:2 complex of chloranilic acid and pyridazine (1,2-diazine), where a short hydrogen bond with N···O distance 2.582 (3) Å is found and the H atom in the hydrogen bond is located near the centre of N···O (Ishida & Kashino, 1999). In the present study, we have prepared the 1:2 complexes of pyrimidine (1,3-diazine) and pyrazine (1,4-diazine), which are isoelectric with pyridazine, and determined the crystal structures at room temperature to investigate the hydrogen bond.



(1)



(2)

In (1), the two components, $C_4H_4N_2$ and $C_6H_2Cl_2O_4$, are held together by strong O—H···N hydrogen bonds [O1—H1 1.07 (4), H1···N1 1.57 (4), O1···N1 2.615 (2) Å and O1—H1···N1 165 (4)°] and stacked in columns along the *a* axis (Fig. 1). In addition, a weak intramolecular O—H···O hydrogen bond is observed [H1···O2^i 2.33 (4), O1···O2^i 2.690 (2) Å and O1—H1···O2^i 98 (3)°; symmetry code: (i) $2-x$, $1-y$, $1-z$]. The cell constants and crystal structure are similar to those of the pyridazine complex.

In (2), the two components are also stacked in columns along the *a* axis, but the packing arrangement of the hydrogen-bonded complex is different from (1) as shown in Fig. 2. The hydrogen bond between the two components is strong [O2—H1 1.06 (5), H1···N1 1.55 (5), O2···N1 2.590 (4) Å and O2—H1···N1 165 (5)°], while the intramolecular hydrogen bond is weak [H1···O1^i 2.33 (6), O2···O1^i 2.693 (4) Å and O2—H1···O1^i 98 (4)°; symmetry code: (i) $2-x$, $-y$, $1-z$].

The interplanar angles between the rings in chloranilic acid and diazines are 12.4 (7), 52.4 (3) and 52.4 (4)°